Study Protocol

A Randomized, Open-Label, Parallel-Group Study to Evaluate the Safety and Efficacy of Two Dosing Regimens of Netarsudil Ophthalmic Solution in Patients with Corneal Edema Due to Fuchs Corneal Dystrophy

NCT 04498169

Protocol Amendment 1 (Rev 1) 03 February 2021

Clinical Study Protocol

Study Title:	A Randomized, Open-Label, Parallel-Group Study to Evaluate the Safety and Efficacy of Two Dosing Regimens of Netarsudil Ophthalmic Solution in Patients with Corneal Edema Due to Fuchs Corneal Dystrophy
Study Number:	AR-13324-CS210
Study Phase:	2
Product Name:	Netarsudil Ophthalmic Solution 0.02%
Indication:	Corneal edema due to Fuchs Corneal Dystrophy (FCD)
Investigators:	Multicenter
Sponsor:	Aerie Pharmaceuticals, Inc. 550 Hills Drive, 3rd Floor Bedminster, NJ 07921 (908) 470-4320
Medical Monitor:	Richard A. Lewis, MD Phone: (916) 768-7703 Email: rlewis@aeriepharma.com
NCT Number	04498169

	Date
Original Protocol (Rev 0):	14 August 2020
Protocol Amendment 1 (Rev 1)	03 February 2021

Confidentiality Statement

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CLINICAL PROTOCOL APPROVAL FORM

Protocol Title: A Randomized, Open-Label, Parallel-Group Study to Evaluate the Safety and Efficacy of Two Dosing Regimens of Netarsudil Ophthalmic Solution in Patients with Corneal Edema Due to Fuchs Corneal Dystrophy

Study No: AR-13324-CS210

Original Protocol Date: 14 August 2020

Protocol Version No: Rev. 1

Protocol Version Date: 03 February 2021

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Signature Date

SYNOPSIS

Sponsor:
Aerie Pharmaceuticals, Inc.

Name of Finished Product:
Netarsudil Ophthalmic Solution 0.02%

Name of Active Ingredients:
Netarsudil mesylate

Study Title:
A Randomized, Open-Label, Parallel-Group Study to Evaluate the Safety and Efficacy of Two Dosing Regimens of Netarsudil Ophthalmic Solution in Patients with Corneal Edema Due to Fuchs Corneal Dystrophy

Study Number:
AR-13324-CS210

Study Phase:
2

Primary Objective:

To evaluate the reduction in central corneal thickness (CCT) in eyes dosed with either Netarsudil Ophthalmic Solution 0.02% (netarsudil) once-daily (QD) or netarsudil twice-daily (BID) for the treatment of corneal edema due to Fuchs corneal dystrophy (FCD).

Secondary Objectives:

(1) To evaluate the proportion of subjects demonstrating improvement in vision following treatment for FCD with netarsudil QD or netarsudil BID.

(2) To evaluate the safety of netarsudil QD and netarsudil BID in subjects with FCD.

Study Design:

This is an 8-week, randomized, open-label, multicenter, efficacy and safety study in subjects with FCD. The study will be conducted at approximately 20 sites in the USA. Two different dosing regimens (QD and BID) of netarsudil will be studied (randomized 1:1) to evaluate their efficacy in reducing or resolving corneal edema in subjects with FCD. Subjects randomized to the netarsudil QD dosing regimen will be instructed to instill one drop of the Study Artificial Tear in the study eye every morning, and one drop of netarsudil in the study eye every evening. Subjects randomized to the netarsudil BID dosing regimen will instill one drop of netarsudil in the study eye every morning and evening.

CCT will be measured by ultrasound pachymetry at approximately the same time of day ± 60 minutes and always before noon (local time), at each of the 5 scheduled visits (Screening, Baseline [Day 1], Week 2, Week 4, and Week 8/Exit). In order to be eligible to participate in the study, subjects will have been diagnosed with visually significant central corneal edema due to FCD, in at least one eye at Screening and Baseline, for no longer than 12 months' duration.

For analysis purposes, the study eye will be defined as the eligible eye with a Baseline CCT of at least 600 µm, as assessed by ultrasound pachymetry. If both eyes are eligible at both Screening and Baseline based on CCT and enrollment criteria, the study eye will be the eye with the thinner cornea at the Baseline Visit.

Study Population:

Approximately forty (40) subjects will be enrolled

Key Inclusion Criteria:

- Adults aged 18 years or older
- Documented diagnosis of FCD

- Evidence of central corneal edema, in at least one eye, at the Screening and Baseline Visit. The study eligible eye(s) should have a CCT of at least 600 µm at both the Screening and Baseline Visit
- Best Corrected Visual Acuity (BCVA) using the Early Treatment of Diabetic Retinopathy Study (ETDRS) methodology of 70 to 20 letters at Screening and Baseline in the eligible eye(s)

Key Exclusion Criteria:

- FCD so advanced that, in the opinion of the Investigator, surgery would likely be required in the study eligible eye(s) within the study period
- Clinically significant ocular disease (other than FCD) or trauma in the eligible eye(s) which could interfere with study interpretation
- History of ocular surgery within 6 months of the Screening Visit, or any prior corneal refractive surgery in the eligible eye(s)

Study Medication, Dose, and Mode of Administration:

Once Daily Netarsudil Dosing Regimen

Study Artificial Tear; one drop, in the study eye in the morning

Netarsudil 0.02% ophthalmic solution; one drop, in the study eye in the evening

Twice Daily Netarsudil Dosing Regimen

Netarsudil 0.02% ophthalmic solution; one drop, in the study eye in the morning and in the evening

Duration of Treatment:

Eight (8) Weeks

Efficacy Assessments:

Primary Endpoint:

- Mean change from baseline in CCT as assessed by ultrasound pachymetry at Week 4

Secondary Endpoints:

- Mean change from baseline in BCVA at Week 4
- Mean change from baseline in CCT as assessed by ultrasound pachymetry at Week 8
- Mean change from baseline in BCVA at Week 8
- Proportion of subjects who gained ≥15 letters (3 lines) in BCVA at Week 4
- Proportion of subjects who gained ≥15 letters (3 lines) in BCVA at Week 8
- Proportion of subjects with complete resolution of corneal edema at Week 4
- Proportion of subjects with complete resolution of corneal edema at Week 8

Safety Assessments:

The safety of netarsudil QD and BID will be evaluated at each visit by:

- Adverse events
- BCVA
- Anterior segment biomicroscopy
- Ophthalmoscopy
- Vital signs (heart rate and blood pressure)
- Intraocular pressure

Statistical Methods:

Continuous study assessments will be summarized by treatment and time point (as applicable) using descriptive statistics (n, mean, median, standard deviation, minimum, and maximum). Categorical study assessments will be summarized by treatment and visit (as applicable) using frequency counts and percentages.

Hypothesis:

H_{01}: The mean change from baseline CCT by ultrasound pachymetry in study eyes treated with netarsudil QD at Week 4 = 0.

H_{11}: The mean change from baseline CCT by ultrasound pachymetry in study eyes treated with netarsudil QD at Week 4 $\neq$ 0.

H_{02}: The mean change from baseline CCT by ultrasound pachymetry in study eyes treated with netarsudil BID at Week 4 = 0.

H_{12}: The mean change from baseline CCT by ultrasound pachymetry in study eyes treated with netarsudil BID at Week 4 $\neq$ 0.

Analysis of Primary Endpoint:

The primary comparisons in this trial will be within a treatment group on the mean change from baseline CCT to Week 4 for each of netarsudil QD and BID. The primary efficacy endpoint change from baseline CCT will be summarized descriptively (n, mean, standard deviation, median, min, and max) and analyzed primarily using one-sample t-tests; comparisons between treatment groups will be completed using two-sample t-tests. Sensitivity analyses will be completed using Wilcoxon signed-rank tests within a treatment group, Wilcoxon rank sum tests between treatment groups and an ANCOVA model with terms for baseline CCT value and treatment. The least squares mean will be presented for each treatment group from the model together with two-sided p-values and 90% and 95% confidence intervals around the change from baseline within each treatment group. Comparisons between treatment groups on the change from baseline CCT will also be made including the least squares mean difference and corresponding two-sided p-values and 90% and 95% confidence intervals.

The primary analysis will use the modified Intent to Treat (mITT), population with available data per subject. Robustness analyses will also be presented based on the multiple imputation methodology under different assumptions of missingness (at random and not at random), using last observation carried forward (LOCF), and using the per protocol population with available data per subject.

Intercurrent events will be primary handled in the following manner:

- Discontinuation of study medication and non-optimal compliance will be ignored [treatment policy strategy].
- Withdrawal due to lack of efficacy or adverse events: missing data will be singly imputed as the worst within subject observation prior to the intercurrent event [hypothetical strategy].
- Missing data without withdrawal or withdrawal due to reasons other than lack of efficacy or adverse events: missing data will be imputed employing Multiple Imputation (MI) using randomized treatment-based Markov Chain Monte Carlo (MCMC) methodology to impute non-monotone missing data and regression methodology to impute monotone missing data [hypothetical strategy].

Safety: Adverse events (AEs) will be coded using the MedDRA dictionary. Frequencies and percentages of treatment emergent adverse events (TEAEs) will be summarized at the subject level by system organ class and preferred term for all TEAEs, treatment related TEAEs, serious TEAEs, and TEAEs causing premature discontinuation by treatment group. An AE is treatment emergent if it occurs or worsens after the first dose of study medication. Similar summaries will be presented for all TEAEs by maximal severity. Separate summaries will be performed for ocular and non-ocular AEs. Other safety endpoints including visual acuity, anterior segment biomicroscopy, intraocular pressure, ophthalmoscopy, and vital signs will be summarized by treatment group and visit using descriptive statistics. Changes or shifts from baseline will also be summarized where appropriate. For assessments performed by eye, study eye and fellow eye will be summarized separately.
Date of Original Approved Protocol (Rev 0): 14 August 2020
Date of Most Recent Protocol Amendment (Rev 1): 03 February 2021

SCHEDULE OF VISITS AND PROCEDURES

Study procedures are recommended to be performed in the sequence specified in the schedule below.

Table 1 Schedule of Visits and Procedures

Visit[1]	**Screening Visit**[1]	**Baseline Visit**[1]	**Week 2**[1]	**Week 4**[1]	**Week 8/Exit**[1]
Visit Window (Days)	**Day -8 to -1**	**Day 1**	**Day 14 ± 3**	**Day 28 ± 3**	**Day 56 ± 3**
Visit Sequence Number	**1**	**2**	**3**	**4**	**5**
Informed Consent	X				
Inclusion/Exclusion	X	X			
V-FUCHS Questionnaire		X		X	X
Demography	X				
Medical/Ophthalmic History	X	X			
Concomitant Medications	X	X	X	X	X
HR/BP	X	X			X
Urine Pregnancy Test[2]		X			X
Ocular Symptoms/AEs	OU	OU	OU	OU	OU
BCVA (ETDRS protocol)	OU	OU	OU	OU	OU
Biomicroscopy	OU	OU	OU	OU	OU
Ultrasound Pachymetry (CCT) [3]	OU	OU	OU	OU	OU
IOP	OU	OU	OU	OU	OU
Dilated Ophthalmoscopy	OU				OU
Undilated Ophthalmoscopy		OU	OU	OU	
Tomography (Pentacam®)[4]	OU	OU	OU	OU	OU
SE Determination[5] and Randomization		X			
Eye Drop Instruction and Demonstration		SE			
Dispense Study Medication		X		X	

Abbreviations: AEs = adverse events; BCVA = best corrected visual acuity; BP = blood pressure; CCT = central corneal thickness; ETDRS = Early Treatment Diabetic Retinopathy Study; HR = heart rate; IOP = intraocular pressure; OU = both eyes; SE = Study Eye; V-FUCHS = Visual Function and Corneal Health Status

1 Subjects should be scheduled at approximately the same time of day ± 60 mins in the morning (ideally at or before 10:00 AM local time) for each visit

2 Required only for females of childbearing potential

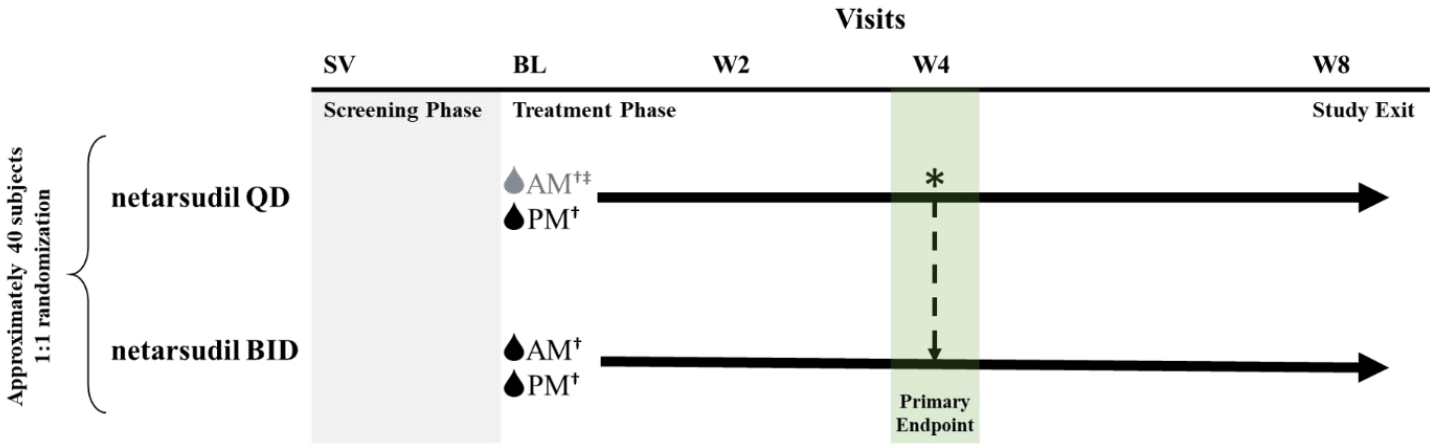
3 Ultrasound pachymetry should be performed at approximately the same time of day ± 60 mins and always before noon local time

4 Selected sites only, may be completed prior to ophthalmoscopy at the Screening and Week 8/Exit Visit while the subject is dilating

5 Please refer to Section 4.4 for instructions on study eye determination

SCHEMA

Figure 1 Study Design Schema



* Any subject randomized to netarsudil QD who, in the opinion of the Investigator, has not responded adequately to treatment, may have their netarsudil dosing frequency increased to BID for the remainder of the study.
† Study eye only. AM dosing should occur between 06:00 and 09:00 hours. PM dosing should occur between 19:00 and 22:00 hours.
‡ Subjects randomized to the netarsudil QD dosing regimen will be instructed to instill one drop of the Study Artificial Tear in their study eye every morning, and one drop of netarsudil in their study eye every evening.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	Adverse Event
AESI	Adverse Event of Special Interest
BCVA	Best Corrected Visual Acuity
BID	Twice Daily
BP	Blood Pressure
CCT	Central Corneal Thickness
CNO	Certificate of Non-Objection
CONMED	Concomitant Medication
DSMC	Data and Safety Monitoring Committee
DSO	Descemet Stripping Only
DWEK	Descemetorhexis Without Endothelial Keratoplasty
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
ETDRS	Early Treatment Diabetic Retinopathy Study
FCD	Fuchs Corneal Dystrophy
GCP	Good Clinical Practice
HR	Heart Rate
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IOP	Intraocular Pressure
IRB	Institutional Review Board

IRT	Interactive Response Technology
kg	Kilogram
L	Liters
mg	Milligram
min	Minute
mmHg	Millimeters Mercury
QD	Once Daily
ROCK	Rho Kinase
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SSAR	Serious Suspected Adverse Reaction
V-FUCHS	Visual Function and Corneal Health Status
WHO	World Health Organization

1. INTRODUCTION

Fuchs Corneal Dystrophy (FCD) is a slowly progressing disease of the cornea that is the most common indication for corneal-endothelial transplants worldwide (Gain 2016). FCD is characterized by corneal edema and the presence of guttae, which are collagenous excrescences of Descemet's membrane (McLaren 2014). As FCD progresses, corneal-endothelial cell degeneration compromises the ability of the cornea to pump out excess fluid resulting in corneal edema and clouding (Okumura 2018). Patients with FDC typically present with glare, blurry vision, and a hazy cornea. Decreased visual acuity may be more pronounced in the morning due to increased corneal hydration that occurs from closed eyelids overnight. In later stages of the disease, edema may reach the corneal epithelium leading to an irregular surface and painful bullae (Moshirfar 2020).

Currently, the only definitive treatment option for FCD is surgery, and endothelial keratoplasty using donor corneas is the gold standard. A newer surgical procedure, called Descemet Stripping Only (DSO) or Descemetorhexis Without Endothelial Keratoplasty (DWEK), is available for select patients and does not require donor corneal tissue. Despite recent improvements in surgical techniques, there are still many risks associated with these procedures including infection, cataract formation, secondary ocular hypertension (OHT) from long term steroid use, graft rejection, and treatment failure requiring a second surgery (Moshirfar 2020). Therefore, there is a large unmet medical need for pharmacologic alternatives to surgery for treating FCD (Koizumi 2014).

Netarsudil is a novel Rho kinase (ROCK) inhibitor that was approved for marketing as Rhopressa® (netarsudil ophthalmic solution) 0.02% by the US FDA in December 2017 for the reduction of elevated intraocular pressure in patients with open-angle glaucoma or OHT.

In addition to lowering intraocular pressure, ROCK inhibitors, such as netarsudil, may also have potential benefit for the treatment of corneal endothelial decompensation. Although the mechanisms are still being elucidated, preclinical evidence is emerging that ROCK inhibition can promote adhesion, enhance proliferation, and inhibit apoptosis of corneal-endothelial cells (Okumura 2009, Okumura 2017). Findings from a clinical case series suggest that topical administration of the ROCK inhibitor Y-27632 after performing transcorneal freezing can improve central corneal edema in patients with FCD (Okumura 2013). In one patient, full corneal transparency was achieved for more than 6 years, and original plans for corneal transplantation were cancelled (Koizumi 2013, Okumura 2018). An additional two case reports of patients with FCD have described improvements in corneal edema and corneal endothelial cell counts with the use of netarsudil following DSO (Ploysangam 2019, Hirabayashi 2020). Several clinical trials are now ongoing to investigate ROCK inhibition in both pre-surgical (NCT04051463) and post-surgical (NCT03575130, NCT03813056, NCT03249337, NCT03971357, NCT04250207, NCT04057053) FCD patients.

Overall, netarsudil is well tolerated, and the most common adverse event is conjunctival hyperemia. Several case reports of honeycomb or reticular edema have been observed in patients taking netarsudil, both with and without pre-existing corneal edema or a history of

FCD (Fernandez 2018, Liu 2019, Moumneh 2020, Wisely 2020). Typically, reticular or honeycomb edema resolves after discontinuation of netarsudil.

The aim of this study is to evaluate the therapeutic potential of netarsudil as a pharmacologic agent to delay or prevent the need for surgery in patients with visually significant edema due to FCD.

2. STUDY OBJECTIVES

2.1 Primary Objective(s)

To evaluate the reduction in central corneal thickness (CCT) in eyes dosed with either netarsudil once-daily (QD), or netarsudil twice-daily (BID) for the treatment of corneal edema due to Fuchs corneal dystrophy (FCD).

2.2 Secondary Objective(s)

(1) To evaluate the proportion of subjects demonstrating improvement in vision following treatment for FCD with netarsudil QD or netarsudil BID.

(2) To evaluate the safety of netarsudil QD and netarsudil BID in subjects with FCD.

3. INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

This is an 8-week, randomized, open-label, multicenter, efficacy and safety study in subjects with FCD. The study will be conducted at approximately 20 sites in the USA. Two different dosing regimens (QD and BID) of netarsudil will be investigated for their efficacy in reducing or resolving corneal edema in subjects with FCD. Subjects randomized to the netarsudil QD dosing regimen will be instructed to instill one drop of the Study Artificial Tear in their study eye every morning, and one drop of netarsudil in their study eye every evening. Subjects randomized to the netarsudil BID dosing regimen will instill one drop of netarsudil in their study eye every morning and evening.

CCT will be measured by ultrasound pachymetry at approximately the same time of day ± 60 minutes and always before noon (local time), at each of the 5 scheduled visits (Screening, Baseline [Day 1], Week 2, Week 4, and Week 8/Exit). In order to be eligible to participate in the study, subjects will have been diagnosed with visually significant central corneal edema due to FCD, in at least one eye, for no longer than 12 months' duration.

At the Screening Visit, the subject's diagnosis of FCD will be confirmed and CCT measured using an ultrasonic pachymeter. Intraocular pressure (IOP) and Best Corrected Visual Acuity (BCVA) will also be collected.

At the Baseline Visit (Day 1), the eligibility assessments conducted during Screening will be repeated to ensure that the subject meets all criteria for enrollment in the study. The same eye must qualify at both the Screening and Baseline Visit. If qualified, the subject will be provided with the Visual Function and Corneal Health Status (V-FUCHS) patient reported visual disability questionnaire (Wacker 2018). The subject will be randomized (1:1) into the study and provided with study medication. Subjects randomized to the netarsudil QD dosing regimen will be instructed to instill one drop of the Study Artificial Tear in the study eye every morning, and one drop of netarsudil in the study eye every evening. Subjects randomized to the netarsudil BID dosing regimen will instill one drop of netarsudil in the study eye every morning and evening. The subject will also be trained on appropriate techniques for applying eye drops.

At the Week 2 and Week 4 Visits, the subject will return to the study site for efficacy and safety assessments.

At the Week 4 Visit, any subject randomized to netarsudil QD who, in the opinion of the Investigator, has not responded adequately to treatment, may have their netarsudil dosing frequency increased to BID for the remainder of the study. For these subjects, the morning administration of Study Artificial Tear will be terminated.

At the Week 8 Visit, a final assessment of efficacy and safety parameters will be conducted, and the subject will exit the study.

For analysis purposes, the study eye will be defined as the eligible eye with a Baseline CCT of at least 600 µm, as assessed by ultrasound pachymetry. If both eyes qualify at both the Screening and Baseline Visit based on CCT and enrollment criteria, the study eye will be the eye with the thinner cornea at the Baseline Visit.

3.2 Rationale for Study Design and Control Group

Current treatment options for FCD include hyperosmotic saline ophthalmic drops/ointments and surgical procedures. Hyperosmotic saline can provide temporary symptomatic relief by facilitating corneal dehydration. Endothelial keratoplasty using donor corneas is currently the gold standard therapeutic option to restore vision in patients with FCD. Although improvement of surgical techniques has enabled less invasive treatment and better outcomes, corneal transplants require long-term steroid use and are still associated with difficult surgical techniques, graft rejection, acute/chronic cell loss, and worldwide donor cornea shortages (Okumura 2017). A relatively new non-transplant surgical procedure known as Descemet Stripping Only (DSO) or Descemetorhexis Without Endothelial Keratoplasty (DWEK) is also now available for a minority of FCD patients.

A pharmacologic alternative to surgery in patients with FCD would be very beneficial, even if pharmacologic treatment only delays the need for surgery.

This study is designed to investigate the efficacy and safety of netarsudil for the treatment of FCD and to enable optimal study design for further clinical development. The optimal dosing regimen will provide maximum reduction in corneal edema due to FCD with minimal adverse effects.

It should be noted that, since FCD is a slowly progressing disease, surgery is rarely urgent, and patients are often seen multiple times before undergoing surgery. Therefore, an approximate 8 to 9-week delay in surgery for participation in this study is acceptable.

3.3 Study Duration

The expected duration of subject participation is approximately 8 to 9 weeks. This includes a screening period of up to 8 days, followed by a treatment period of 8 weeks.

4. STUDY POPULATION SELECTION

4.1 Study Population

A total of approximately 40 subjects will be enrolled into the study at approximately 20 investigational sites within the United States. Subjects will be at least 18 years of age with a diagnosis of FCD, each of whom meets all inclusion criteria and none of the exclusion criteria listed below.

4.2 Inclusion Criteria

Subjects must meet all of the following criteria to enter into the study:

1. Adults, aged 18 years or older at the Screening Visit, of either sex and any race or ethnicity

2. Documented diagnosis of FCD at the Screening Visit

3. Evidence of central corneal edema, in at least one eye, at the Screening and Baseline Visit. The study eligible eye(s) should have a CCT of at least 600 μm at both Screening and Baseline, as assessed by ultrasound pachymetry

4. Evidence of corneal edema attributed to FCD of <12-months' duration in the eligible eye(s)

5. Best Corrected Visual Acuity using the Early Treatment of Diabetic Retinopathy Study (ETDRS) methodology of 70 to 20 letters at Screening and Baseline in the eligible eye(s)

6. Presence of central corneal edema deemed by the Investigator to be the chief cause of reduced visual acuity in the eligible eye(s)

7. Willing and able to provide written informed consent to participation in the study prior to any and all study-related activities

4.3 Exclusion Criteria

Subjects meeting any of the following criteria will be excluded from entry into the study:

Ophthalmic:

1. FCD so advanced that, in the opinion of the Investigator, surgery would likely be required in the study eligible eye(s) within the study period
2. Concurrent or anticipated need for treatment for FCD, e.g., Muro 128 (2% or 5%) during the course of the study in the study eligible eye(s). Provided the subject undergoes a washout of Muro drops for at least 24 hours prior to the Baseline Visit, they will not be excluded
3. Clinically-significant ocular disease or trauma which could interfere with the interpretation of study results (e.g., uveitis, scarring, any severe retinal disease) in the eligible eye(s)
4. Recent (within 3 months of Screening) or current ocular infection (bacterial, fungal or viral) in either eye
5. Recent (within 3 months of Screening) or current severe ocular inflammation (e.g., severe blepharitis, conjunctivitis) in either eye
6. History of any prior ocular refractive surgery in the study eligible eye(s)
7. Use of contact lenses in either eye within 7 days prior to the Baseline Visit or planned use during the study
8. History of ocular surgery within 6 months of the Screening Visit, any prior complicated cataract surgery resulting in vitreous loss, or any anticipated ocular surgery during the course of the study in the study eligible eye(s)
9. Current treatment for, or a history of severe or difficult to treat (i.e., requiring ≥3 ocular hypotensive medications) glaucoma (open- or closed- angle) or OHT. Fixed dose combination medications will be considered as two medications
10. Concurrent use of oral or ophthalmic carbonic anhydrase inhibitors (e.g., acetazolamide [Diamox®], dorzolamide [Trusopt®], or brinzolamide [Azopt®]) during the course of the study is prohibited. Individuals currently on, or previously treated with, oral carbonic anhydrase inhibitors for IOP reduction will be excluded from the study. Individuals currently using ophthalmic carbonic anhydrase inhibitor drops must undergo a minimum washout period of 5 days prior to the Baseline Visit
11. Concurrent or anticipated use of topical corticosteroids in the study eligible eye(s)
12. History of prior treatment with netarsudil (monotherapy or in combination) or any other topical ocular Rho Kinase inhibitor

Systemic:

13. Any clinically-significant or chronic co-morbidity which, in the opinion of the Investigator, could interfere with the subject's ability to participate in the study and comply with the protocol, visit schedule and all assessments (e.g., autoimmune disorder, terminal illness, psychiatric or cognitive disorder, severe cardiac, pulmonary, or neurological condition, advanced diabetes, etc.)

14. Known contraindication or hypersensitivity to any of the treatments, anesthetics or diagnostic agents or components thereof which may be used during the study

15. Recent (within 60 days of the Screening Visit) or ongoing participation in any other investigational interventional clinical study

16. Concurrent or anticipated use of systemic corticosteroids during the study. Individuals currently using topical or other locally acting corticosteroids (with the exception of use in the study eligible eye[s]) must have been on a stable dose for at least 30 days prior to the Screening Visit, and the dose must not be anticipated to change during the course of the study

17. Women of child-bearing potential who are pregnant, nursing, planning a pregnancy or not using a medically acceptable form of birth control (to be considered **NOT** of child-bearing potential, a woman must be at least one-year post-menopause or three-months post-surgical sterilization). All women of child-bearing potential will be required to take a urine pregnancy test at the Screening and Week 8/Exit Visits

Subjects who have transient, fluctuating edema, but otherwise meet all of the inclusion criteria and none of the exclusion criteria WILL be allowed into the study.

4.4 Study Eye Determination

The subject must have at least one eye meeting all the inclusion criteria (Section 4.2) and none of the exclusion criteria (Section 4.3) at the Screening and Baseline Visit. The study eligible eye(s) should have a Screening and Baseline CCT of at least 600 μm, as assessed by ultrasound pachymetry. If both eyes qualify at both the Screening and Baseline Visit, the study eye will be the eye with the thinner cornea at the Baseline Visit. If both eyes have the same CCT, the study eye will be the right eye. Study subjects will be instructed to instill the study medication into the study eye only.

5. STUDY TREATMENTS

5.1 Description of Treatments

5.1.1 Study Medication

Netarsudil is a ROCK inhibitor approved by the US Food and Drug Administration for the treatment of OHT and open-angle glaucoma.

Netarsudil 0.02% ophthalmic solution is supplied as a sterile, isotonic, buffered aqueous solution of netarsudil dimesylate with a pH of approximately 5 and an osmolality of approximately 295 mOsmol/kg. It is intended for topical application in the eye. Each mL contains 0.2 mg of netarsudil (equivalent to 0.28 mg of netarsudil dimesylate). Benzalkonium chloride, 0.015%, is added as a preservative. The inactive ingredients are boric acid, mannitol, sodium hydroxide to adjust pH, and water for injection.

5.1.2 Placebo or Control Drug

A Study Artificial Tear will be provided to subjects randomized to the QD dosing regimen. These subjects will be instructed to instill one drop of the Study Artificial Tear every morning.

The Study Artificial Tear will be REFRESH PLUS® (preservative-free) Lubricant Eye Drops. The active ingredient is carboxymethylcellulose sodium (0.5%), and the inactive ingredients are calcium chloride, magnesium chloride, potassium chloride, purified water, sodium chloride, and sodium lactate. The solution may also contain hydrochloric acid and/or sodium hydroxide to adjust pH.

5.2 Treatments Administered

Subjects will be randomized using a 1:1 allocation ratio to one of two treatment groups:

- Once Daily Netarsudil Dosing Regimen

  Study Artificial Tear; one drop, in the study eye in the morning

  Netarsudil 0.02% ophthalmic solution; one drop, in the study eye in the evening

- Twice Daily Netarsudil Dosing Regimen

  Netarsudil 0.02% ophthalmic solution; one drop, in the study eye in the morning and in the evening

Doses will be self-administered by the study subjects. If the subject is using any another topical ophthalmic drop (e.g., ocular hypotensive medications) at the same time as netarsudil, the subject should be instructed to instill netarsudil first, and wait at least 15 minutes before instilling any additional drops.

For subjects deemed unable to self-administer the doses, a caregiver will be asked to administer the medication. All subjects will administer study medication for approximately 8 weeks.

5.3 Selection and Timing of Dose for Each Patient

The dose and regimens selected for this study have previously been tested in studies of netarsudil for the treatment of glaucoma and OHT.

5.4 Method of Assigning Patients to Treatment Groups

Subjects will be assigned to treatment groups through the use of an interactive response technology (IRT) system.

5.5 Masking

This is an open-label study.

5.6 Concomitant Therapy

5.6.1 Prohibited Interventions

Concomitant use of hypertonic sodium chloride ophthalmic solution (e.g., Muro 128 [2% or 5%]) during the course of the study is prohibited. Individuals currently using hypertonic sodium chloride drops or ointment must undergo a minimum washout period of 24-hours prior to the Baseline Visit.

Concomitant use of oral or ophthalmic carbonic anhydrase inhibitors (e.g., acetazolamide [Diamox®], dorzolamide [Trusopt®], or brinzolamide [Azopt®]) during the course of the study is prohibited. Individuals currently on, or previously treated with, oral carbonic anhydrase inhibitors for IOP reduction will be excluded from the study. Individuals currently using ophthalmic carbonic anhydrase inhibitor drops must undergo a minimum washout period of 5 days prior to the Baseline Visit.

Concomitant use of systemic corticosteroids is prohibited during the course of the study. Individuals currently using topical or other locally acting corticosteroids (with the exception of use in the study eligible eye[s]) must have been on a stable dose for the month prior to the Baseline Visit, and the dose must not be anticipated to change during the course of the study.

Contact lens wear in either eye during the course of the study is prohibited. Individuals currently wearing contact lenses must undergo a minimum washout period of 7 days prior to the Baseline Visit.

The use of subject's own artificial tears will not be permitted. All subjects will be provided with a Protocol Approved Artificial Tear for intermittent use, up to four times daily. See Section 5.6.2 for more information on the Protocol Approved Artificial Tear.

5.6.2 Permitted Interventions

Therapy considered necessary for the subject's welfare may be given at the discretion of the Investigator. If the use of a specific therapy or intervention is in question, please contact Aerie.

Any systemic medication not itemized as an exclusion in Section 4.3 (i.e., oral carbonic anhydrase inhibitors or systemic corticosteroids) will be permitted.

Any topical ophthalmic medication not itemized as an exclusion in Section 4.3 (i.e., hypertonic saline, ophthalmic carbonic anhydrase inhibitors, or ophthalmic corticosteroids in the study eye) will be permitted. Ocular hypotensive medications will be permitted, however, a history of severe or difficult to treat (i.e., requiring ≥3 ocular hypotensive medications) glaucoma (open- or closed- angle) or OHT will exclude a subject from participation in this study. Fixed dose combination medications will be considered as two medications. If multiple topical ophthalmic medications are needed at the same time, subjects should be instructed to always instill netarsudil first and wait at least 15 minutes before instilling any additional drops.

The intermittent use of artificial tears will be permitted. However, subjects must use the (Aerie supplied) Protocol Approved Artificial Tear (REFRESH PLUS® [preservative-free]). The Protocol Approved Artificial Tear may be used, as needed, up to four times daily (QID) in either eye. If the subject intends on using the Protocol Approved Artificial Tear at the same time as their scheduled netarsudil dose, they should be instructed to instill netarsudil first and wait a minimum of 15 minutes before instilling the Protocol Approved Artificial Tear.

Any medication taken during the study between the date of the first dose of randomized study medication and the date of the Week 8/Exit Visit or Early Termination Visit should be recorded in the eCRF as a concomitant medication.

5.7 Restrictions

5.7.1 Prior Therapy

Prior use of netarsudil (monotherapy or in combination) will exclude the patient from participation in the study.

5.7.2 Fluid and Food Intake

There are no fluid or food intake restrictions for subjects participating in this study.

5.7.3 Subject Activity Restrictions

There are no activity restrictions for subjects participating in this study.

5.8 Treatment Compliance

All subjects will be instructed on the importance of following their assigned dosing regimen. Subjects in the once daily netarsudil treatment group will instill one drop of the Study Artificial Tear in the study eye every morning, and one drop of netarsudil 0.02% in the study eye every evening. Subjects in the twice daily netarsudil treatment group will instill one drop of netarsudil 0.02% in the study eye in the morning and evening. At Week 4, any subject randomized to netarsudil QD who, in the opinion of the Investigator, has not responded adequately to treatment, may have their netarsudil dosing frequency increased to BID for the remainder of the study.

Morning dosing should occur between 06:00 and 09:00 hours. Evening dosing should occur between 19:00 and 22:00 hours.

As no commercial method is readily available for direct single-container monitoring of treatment adherence with multi-dose ophthalmic products, no formal measure of treatment adherence to netarsudil is planned.

Subjects should be reminded at all visits to adhere to their assigned dosing regimen.

5.9 Packaging and Labeling

Netarsudil will be supplied in a sterile, clear, multi-dose low density polyethylene (LDPE) dropper dose ophthalmic bottle with a white propylene cap.

The Study Artificial Tear (REFRESH PLUS® [preservative-free]) will be supplied in a box containing 30 single use containers.

The Protocol Approved Artificial Tear (REFRESH PLUS® [preservative-free]) will be supplied in a box containing 30 single use containers. Please see Section 5.6.2 for more information on the Protocol Approved Artificial Tear.

5.10 Storage and Accountability

The study medication, Study Artificial Tears, and Protocol Approved Artificial Tears must be dispensed according to the procedures prescribed in this protocol. Only subjects enrolled in the study may receive study medication, in accordance with all the applicable regulatory requirements. Only authorized staff is allowed to dispense these medications.

Under normal conditions of handling and administration, the study medication, Study Artificial Tears, and Protocol Approved Artificial Tears are not expected to pose significant safety risk to site staff. Adequate precautions must be taken to avoid direct contact with the study medication.

The study medication, Study Artificial Tears, and Protocol Approved Artificial Tears will be stored in a secure area under the appropriate physical conditions for the product. Access to the study medication, Study Artificial Tears, and Protocol Approved Artificial Tears will be limited to authorized site staff only. The study medication and artificial tears will be stored as directed on the label. Netarsudil should be stored refrigerated (2°C to 8°C / 36°F to 46°F) and protected from light. Study Artificial Tears and Protocol Approved Artificial Tears will be stored between 15°C and 30°C (59°F and 86°F). Temperature of the study medication storage locations at the site is to be monitored using a calibrated monitoring device and documented.

At time of dispensing, the subject will be instructed to store the bottle(s) as directed on the label. Once the netarsudil bottle is opened, the product must always be stored refrigerated and protected from light. It is recommended that the product is stored in the carton provided.

5.11 Study Medication Retention at Study Site

5.11.1 Receipt and Disposition of Study Medication

Study medication and artificial tears (Study Artificial Tears and Protocol Approved Artificial Tears) will be shipped to the Investigator's site from a central depot. A study staff member at the Investigator's site will verify study medication shipment records by comparing the shipping documentation accompanying the study medication to the study medication received at the Investigator's site. If a discrepancy is noted, the appropriate individual at the Sponsor or designee must be notified immediately. The responsible person (e.g., study coordinator) at the Investigator's institution has to account for all used, partially used, and unused study medication and artificial tears. The responsible person will also maintain the study medication accountability records.

5.11.2 Return of Study Medication

When the site is closed, the study is completed or is terminated by the Sponsor; all study material including used and unused study medication and artificial tears will be returned to the Sponsor's designee. All study medication accounting procedures must be completed before the study is considered to be concluded. The responsible person at the Investigator's institution has to account for all used, partially used and unused study medication and artificial tears. The monitor will complete a study medication returns form or equivalent that will be signed by the Investigator or designee prior to returning the used and unused study medication and artificial tears to the Sponsor's designee.

6. STUDY PROCEDURES

6.1 Informed Consent

Prior to any study procedures in the treatment period, the study will be discussed with each subject. Subjects wishing to participate must give written informed consent. The verbal explanation of the study will cover all the elements specified in the written information provided for the subject. The Investigator will inform the subject of the aims, methods, anticipated benefits and potential hazards of the study, including any discomfort it may entail. The subject must be given every opportunity to clarify any points he/she does not understand and, if necessary, may ask for more information. At the end of the interview, the subject should be given time to reflect. Subjects and/or legally authorized representative then will be required to sign and date the informed consent form. The completion of this process should be documented in the source documents.

The informed consent form must have received approval/favorable review by a properly constituted Institutional Review Board/Independent Ethics Committee (IRB/IEC) prior to use. A copy of the signed and dated consent document will be given to each subject.
The original signed and dated informed consent document must be maintained in the study files at the Investigator's site.

The Investigator or staff is responsible for ensuring that no subject undergoes any study related examination or activity before the subject has given written informed consent.
It should be emphasized that the subject is at liberty to withdraw consent to participate at any time, without penalty or loss of benefits to which the subject is otherwise entitled. Subjects who refuse to give, or withdraw, written informed consent may not be included or continued in this study, and should be notified that discontinuation from the study will not impact on their subsequent care.

6.2 Demographics and Medical/Ophthalmic History

Demographic data will be collected and recorded at the Screening Visit. Significant, relevant (to the condition under investigation) medical/ophthalmic history will also be collected at Screening and Baseline. Any current underlying medical conditions, including those that began within the last 30 days and which may have resolved before screening, must be recorded. In addition, prior treatments for FCD should be recorded. Any medications the subject took but discontinued within the 30 days prior to screening also will be recorded as part of the medical history.

6.3 Concomitant Medication Assessments

Use of any medication, prescription or over-the-counter (OTC), should be recorded at the Screening Visit, and captured on the appropriate eCRF, and the indication noted as part of the medical history. Treatments that are permitted to continue throughout the duration of the study will be recorded as concomitant medications at all subsequent visits. Judgment of

continued study participation by the subject, and inclusion of this subject's subsequent visits in the safety and efficacy analysis will be made by the Investigator.

All medications which the subject has taken within 30 days prior to screening and during the study will be recorded in the eCRF. The name of the drug, dose, route of administration, duration of treatment and indication will be recorded for each medication. For combination products (e.g., CONTAC®), the brand name is required. For non-combination products, the generic name is preferred. The use of routine ophthalmic diagnostic pharmaceutical agents (e.g., fluorescein) will be allowed, and individual documentation not required. Any change in dosing parameters should also be recorded in the eCRF.

6.4 Vital Signs (HR and BP only)

Subject heart rate and blood pressure will be measured at the Screening, Baseline, and Week 8/Exit Visits. Heart rate will be determined only once during these study visits by the method described in the Study Procedure Manual.

Blood pressure will be measured once for each subject after the subject heart rate has been determined, with the subject in a sitting position. A mechanical or digital sphygmomanometer may be used, but effort should be made to use the same instrument and the same arm of the subject for each reading. Please refer to the Study Procedure Manual for more details.

6.5 Pregnancy Testing

A urine pregnancy test will be conducted at the Baseline Visit and the Week 8/Exit Visit for all females of child-bearing potential. A female of child-bearing potential is defined as an adult woman unless she is 1-year post-menopausal or 3 months post-surgical sterilization. Any female who is pregnant, nursing, planning a pregnancy, or not using a medically acceptable form of birth control will be excluded from the study. All females of childbearing potential must have a negative pregnancy test result at the Baseline Visit to be enrolled and must not intend to become pregnant during the study.

6.6 Dispensing Study Medication

Study staff responsible for dispensing the study medication will be listed on the Delegation of Responsibilities Log. When a subject meets all criteria for selection and has completed all screening assessments, the subject will be assigned to a treatment group according to the IRT.

Study medication, Study Artificial Tears (for subjects randomized to the QD dosing regimen), and Protocol Approved Artificial Tears will be dispensed at the Baseline Visit. Additional study medication, Study Artificial Tears (for subjects randomized to the QD dosing regimen), and Protocol Approved Artificial Tears (if needed) will be dispensed at the Week 4 Visit.

The responsible study staff will account for used and unused study medication and artificial tears by maintaining a study medication accountability log.

6.7 Efficacy Assessments

6.7.1 Ultrasound Pachymetry

CCT will be measured at each visit at approximately the same time of day ± 60 minutes and always before noon (local time). Every effort should be made to use the same instrument for each reading. For more details, please refer to the Study Procedure Manual.

6.7.2 Best Corrected Visual Acuity (ETDRS Method)

At each visit, BCVA should be measured using the ETDRS method, following manifest refraction, and prior to the slit lamp examination. Please refer to the BCVA Procedure Manual for the BCVA Worksheet and more details.

6.7.3 Biomicroscopy

External magnification and biomicroscopy will be performed using a slit-lamp. Magnification will be consistent with standard clinical practice. The subject will be seated.

The following will be examined:

- Eyelid
- Cornea
- Conjunctiva
- Anterior Chamber
- Iris
- Lens

For more details, please refer to the Study Procedure Manual.

6.7.4 V-FUCHS Questionnaire

The Visual Function and Corneal Health Status (V-FUCHS) patient reported visual disability questionnaire will be administered at the Baseline, Week 4, and Week 8 Visits (Wacker 2018). Subjects who are not fluent in the English language may be exempt from completing this questionnaire. Please refer to the Study Procedure Manual for the full 15-item questionnaire and additional details.

6.7.5 Tomography (Pentacam®; Selected Sites Only)

Tomography assessments using a Pentacam® will be performed at selected sites only. Please refer to the Study Procedure Manual for more details.

6.8 Safety Assessments

6.8.1 IOP

At each visit, IOP will be measured using an Applanation Tonometer.

6.8.2 Ophthalmoscopy

Indirect ophthalmoscopy will be performed with pupil dilation at the Screening and Week 8/Exit Visits and without dilation at all other visits. The Investigator will make observations of the vitreous, retina, macula, choroid and optic nerve. Please refer to the Study Procedure Manual for more details.

6.9 Adverse Events Assessments

6.9.1 Performing Adverse Event (AE) Assessments

Qualified study staff responsible for assessing AEs will be listed on the Site Authorization and Delegation Log. This includes assessment of AE severity and relationship to the study medication. AE information may be volunteered by the subject or solicited by study personnel through non-leading questions.

All AEs occurring during the study, regardless of the assumption of causal relationship, must be documented on the respective electronic case report form (eCRF). Adverse events should be documented from the time the subject signs the informed consent until the subject's last study visit. If an event occurs during the washout period (prior to subject enrollment and the administration of study medication), it should be recorded as an AE. Any medical condition present prior to administration of the study medication which remains unchanged or improved should not be recorded as an AE at subsequent visits.

If a subject has an ongoing AE at the time of study completion, the ongoing AE must be followed-up and provided appropriate medical care until the event has resolved or stabilized, the subject is lost to follow-up, or there is other resolution to the event.

Documentation of AEs/adverse reactions includes start date and stop date, severity, action(s) taken, seriousness and outcome.

Investigators are also asked to note all observations of new or worsening conjunctival hyperemia on the biomicroscopy eCRF as well as on the study AE form if deemed necessary (per Investigator discretion).

The following definitions of terms apply to this section:

- Adverse event (AE). Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

- Suspected adverse reaction (SAR). Any AE for which there is a reasonable possibility that the drug caused the AE. For the purposes of IND safety reporting, ‘‘reasonable possibility’’ means there is evidence to suggest a causal relationship between the drug and the AE. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any AE caused by a drug.

- Life-threatening AE or life-threatening SAR. An AE or SAR is considered “life-threatening” if, in the view of either the Investigator or Sponsor, its occurrence places the patient at immediate risk of death. It does not include an AE or SAR that, had it occurred in a more severe form, might have caused death.

- Serious adverse event (SAE) or serious suspected adverse reaction (SSAR). An AE or SAR is considered ‘‘serious’’ if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes: Death, a life-threatening AE, patient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in patient hospitalization, or the development of drug dependency or drug abuse.

- Unexpected AE or unexpected SAR. An AE or SAR is considered ‘‘unexpected’’ if it is not listed in the Investigator’s Brochure (IB), the Package Insert, or is not listed at the specificity or severity that has been observed. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the IB referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the IB listed only cerebral vascular accidents. “Unexpected,” as used in this definition, also refers to AEs or SARs that are mentioned in the IB as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

6.9.2 Timing

The AEs occurring during the study must be documented, regardless of the assumption of a causal relationship. AEs should be documented from the time the subject signs and dates the patient consent form until subject participation in the study has been completed. If a subject has one or more ongoing AEs at the time of study completion, the subject should be followed and provided appropriate medical care until the event is resolved or stabilized, the subject is lost to follow-up, or there is other resolution to the event. These follow-up visits will be documented.

When recording an AE, the following information should be provided on the study AE eCRF:

1. **Action Taken with Study Medication:**

- None
- Study Medication Interrupted
- Study Medication Discontinued

2. **Other Action Taken:**

- None
- Non-Drug Therapy
- New OTC or Rx Drug Added
- Hospitalized less than 24 hours
- Hospitalized greater than or equal to 24 hours

3. **Outcome of an adverse event is coded as:**

- Fatal
- Not Recovered/Not Resolved
- Recovered/Resolved
- Recovered/Resolved with sequelae
- Recovering/Resolving
- Unknown/Lost to follow-up

6.9.3 Severity

Severity of an AE is defined as a qualitative assessment of the level of discomfort or the degree of intensity of an AE as determined by the Investigator or reported to him/her by the subject. The assessment of severity is made irrespective of study medication relationship or seriousness of the event and should be evaluated according to the following scale:

1 = Mild: present and noticeable, but not distressing, and no disruption of normal daily activities.

2 = Moderate: bothersome, discomfort sufficient to possibly reduce or affect normal daily activity.

3 = Severe: incapacitating, with inability to work or perform normal daily activity.

A change in increased severity for a reported AE will require a stop date for the previous severity and a new start and stop date for the new severity. For example, a change in severity may go from mild to severe or from moderate to severe. In both cases, the start and stop dates should be recorded.

Note: A severe AE is not the same as a serious AE. Seriousness of an AE (NOT severity) serves as a guide for defining regulatory reporting obligations (see Section 6.9.6 for further information on serious AEs [SAEs]).

6.9.4 Relationship

The study medication relationship for each AE/adverse reaction should be determined by the Investigator using these explanations:

- **Not Related**: The event is clearly related to other factors such as subject's clinical condition; therapeutic interventions, concomitant disease or therapy administered to the subject and does not follow a known response pattern to the product.

- **Unlikely Related**: The event is most probably caused by other etiologies such as participant's underlying condition, therapeutic intervention, or concomitant therapy; or the delay between administration and the onset of the AE is incompatible with a causal relationship. Therefore, there is not a reasonable possibility that the AE was caused by the study medication.

- **Possibly Related**: The event follows a reasonable, temporal sequence from the time of study medication administration and/or follows a known response pattern to the study medication, but could have been produced by other factors such as the subject's clinical state, therapeutic interventions or concomitant therapy administered to the subject.

- **Related**: The event follows a reasonable, temporal sequence from the time of study medication administration and/or follows a known response pattern to the study

medication and cannot be reasonably explained by other factors such as subject's clinical state, therapeutic interventions or concomitant therapy administered to the subject, and either occurs immediately following study medication administration, or improves on stopping the study medication, or reappears on repeat exposure, or there is a positive reaction at the application site.

6.9.5 Expectedness

An AE or suspected adverse reaction is considered "unexpected" if it is not listed in the IB or is not listed at the specificity or severity that has been observed. "Unexpected," as used in this definition, also refers to adverse events or suspected adverse reactions that are mentioned in the IB as occurring with this class of drugs or as anticipated from the pharmacological properties of netarsudil, and are not specifically mentioned as occurring with the study medication. The AEs and adverse reactions that are both unexpected and serious should be reported in an expedited fashion to the Sponsor (see Section 6.9.6 for further details).

6.9.6 Serious Adverse Events, Suspected Serious Adverse Reactions or Suspected Unexpected Serious Adverse Reactions

6.9.6.1 Reporting SAEs, SSARs or SUSARs

An Investigator must immediately (i.e., within 24 hours) report any SAE, SSAR or SUSAR to the Sponsor using the SAE report form, whether or not considered medication-related, including those listed in the IB, and must include an assessment of whether there is a reasonable possibility that the medication caused the event. In addition, in the case of immediately life-threatening AEs or AEs with fatal outcome, or SUSARs, the Investigator must inform the Sponsor by phone within 24 hours of observation or occurrence of the SAE.

The Investigator must report any SAE, SSAR, or SUSAR that occurs during the course of the study or within 4 weeks of last study visit. In case of incomplete information, the Investigator must provide follow-up information as soon as possible, again using the SAE report form.

SAEs, SSARs, and SUSARs must be reported to the IRB/IEC according to the IRB/IEC requirements.

The contact information of the study Safety Mailbox is as follows:

Covance PSS
SAEintake@covance.com
Fax: 1-888-887-8097

The contact information of the study Medical Monitors is as follows:

Richard A. Lewis, MD
Phone: (916) 768-7703
Email: rlewis@aeriepharma.com

6.9.7 Pregnancy Reporting

Pregnancies occurring in subjects in this study, occurring up to the subject's last study visit, must be reported and followed to outcome. Information on pregnant partners will not be collected.

While pregnancy itself is not considered to be an AE or SAE, pregnancy reports are tracked by Covance and the study Medical Monitor. Premature terminations including miscarriage, spontaneous abortion, or elective termination of a pregnancy for medical reasons will be reported as an SAE. Other pregnancy complications should be reported as SAEs, if they meet serious criteria. Should a pregnancy result in a congenital anomaly or birth defect, a separate SAE report must be submitted for the baby. Furthermore, all neonatal deaths that occur within 30 days of the birth should be reported as SAEs, without regard to causality.

The Investigator must complete the pregnancy report form and email the form to the study Safety Mailbox within 1 business day of knowledge of the pregnancy. Following delivery or termination of pregnancy, the updated or follow-up pregnancy report form is to be completed and submitted by fax or email to the Safety Mailbox for the study.

6.10 Removal of Subjects from the Study or Study Medication

Subjects may be discontinued from the study at any time for any reason. Participation is entirely voluntary, and only possible if the subject has signed informed consent. Consent may be withdrawn at any time.

6.10.1 Completed Subject

A completed subject is defined as one who completes all planned study treatments and visits.

6.10.2 Non-completing Subject

A non-completing subject is defined as one who exits the study by their own volition or at the discretion of the Investigator, the Medical Monitor, and/or an Aerie Safety Officer/designee. Any subject may decide to voluntarily withdraw from the study at any time without prejudice. If discontinuation of treatment is necessary, the Investigator will make every attempt to complete all subsequent safety assessments listed for the Week 8 / Early Termination Visit.

The subject may also be discontinued from the study for the following reasons:

- AEs (including intercurrent diseases reported by the subject or observed by the Investigator with documentation on the CRF)
- Withdrawal of Consent
- Non-compliance (e.g., non-adherence to scheduled follow-up visits or use of study treatment)

- Lost to Follow-up
- Pregnancy
- Investigator Decision
- Protocol Deviation
- Death
- Other

6.10.3 Actions after Discontinuation

All subjects who discontinue study treatment due to a report of an AE must be followed and provided appropriate medical care until their signs and symptoms have remitted or stabilized.

For subjects who choose to withdraw consent or who are discontinued for non-compliance prior to completing the study, every possible effort should be made by the Investigator to assure there is a final visit that includes all examinations listed for the Week 8 / Early Termination Visit.

6.10.4 Discontinuation of the Entire Study

The entire study may be discontinued at a given site (by the Investigator or Aerie /Aerie representative) or at all sites by Aerie. Prompt, written notice of reasonable cause to all other relevant parties (Aerie or Investigator) is required. Prompt notice to the IRB and to regulatory authorities is also required.

6.10.5 Completed Study

The study is completed when the planned enrollment has been completed, and all the enrolled subjects have completed the study. An Aerie representative will be in communication with the investigational sites regarding enrollment.

6.11 Appropriateness of Measurements

The ophthalmic and systemic measures included in this study are consistent with standard of care.

7. STUDY ACTIVITIES

A detailed Schedule of Visits and Procedures is provided in Table 1. Subjects should be scheduled at approximately the same time of day ± 60 mins in the morning (ideally at or before 10:00 local time) for each visit to ensure that ultrasound pachymetry is completed before noon (local time).

7.1 Screening Visit (Day -8 to -1)

- Informed consent
- Inclusion and exclusion criteria
- Demographics
- Medical, ophthalmic, and surgical history
- Prior or concomitant medication review
- Vital signs (heart rate and blood pressure only)
- Ocular symptoms and AE review for both eyes
- BCVA using the ETDRS method and following manifest refraction for both eyes
- Anterior segment biomicroscopic examination of both eyes
- CCT will be measured by ultrasound pachymetry in both eyes
    - Note: Ultrasound pachymetry should be performed at approximately the same time of day for all visits (± 60 minutes) and always before noon (local time)
- IOP in both eyes
- Dilated Ophthalmoscopy in both eyes
- Tomography (Pentacam®) for both eyes (at selected sites only) – may be performed prior to ophthalmoscopy while the subject is dilating

7.2 Treatment Period

7.2.1 Baseline (Day 1) Procedures

- Inclusion and exclusion criteria
- Visual Function and Corneal Health Status (V-FUCHS) patient reported visual disability questionnaire (Wacker 2018)
- Medical, ophthalmic, and surgical history
- Concomitant medication review
- Vital signs (heart rate and blood pressure only)

- Urine pregnancy test (WOCBP only)
- Ocular symptoms and AE review for both eyes
- BCVA using the ETDRS method and following manifest refraction for both eyes
- Anterior segment biomicroscopic examination of both eyes
- CCT will be measured by ultrasound pachymetry in both eyes
    - Note: Ultrasound pachymetry should be performed at approximately the same time of day for all visits (± 60 minutes) and always before noon (local time)
- IOP in both eyes
- Ophthalmoscopy without dilation in both eyes
- Tomography (Pentacam®) for both eyes (at selected sites only)
- Study eye determination (See Section 4.4)
- Randomization
- Eye drop instruction and demonstration for the study eye
- Dispensing of study medication, Study Artificial Tears (if randomized to the QD dosing arm), and Protocol Approved Artificial Tears

7.2.2 Week 2 (Day 14 ± 3) Procedures

- Concomitant medication review
- Ocular symptoms and AE review for both eyes
- BCVA using the ETDRS method and following manifest refraction for both eyes
- Anterior segment biomicroscopic examination of both eyes
- CCT will be measured by ultrasound pachymetry in both eyes
    - Note: Ultrasound pachymetry should be performed at approximately the same time of day for all visits (± 60 minutes) and always before noon (local time)
- IOP in both eyes
- Ophthalmoscopy without dilation in both eyes
- Tomography (Pentacam®) for both eyes (at selected sites only)

7.2.3 Week 4 (Day 28 ± 3) Procedures

- Visual Function and Corneal Health Status (V-FUCHS) patient reported visual disability questionnaire (Wacker 2018)
- Concomitant medication review
- Ocular symptoms and AE review for both eyes
- BCVA using the ETDRS method and following manifest refraction for both eyes
- Anterior segment biomicroscopic examination of both eyes
- CCT will be measured by ultrasound pachymetry in both eyes
    - Note: Ultrasound pachymetry should be performed at approximately the same time of day for all visits (± 60 minutes) and always before noon (local time)
- IOP in both eyes
- Ophthalmoscopy without dilation in both eyes
- Tomography (Pentacam®) for both eyes (at selected sites only)
- Dispensing of study medication, Study Artificial Tears (if randomized to the QD dosing arm), and Protocol Approved Artificial Tears (if needed)
    - Note: At the Week 4 Visit, any subject randomized to netarsudil QD who, in the opinion of the Investigator, has not responded adequately to treatment, may have their netarsudil dosing frequency increased to BID for the remainder of the study. The subject should be re-trained on their new dosing regimen, if applicable.

7.2.4 Week 8 (Day 56 ± 3) or Early Termination Procedures

- Visual Function and Corneal Health Status (V-FUCHS) patient reported visual disability questionnaire (Wacker 2018)
- Concomitant medication review
- Vital signs (heart rate and blood pressure)
- Urine pregnancy test (WOCBP only)
- Ocular symptoms and AE review for both eyes
- BCVA using the ETDRS method and following manifest refraction for both eyes

- Anterior segment biomicroscopic examination of both eyes
- CCT will be measured by ultrasound pachymetry in both eyes
    - Note: Ultrasound pachymetry should be performed at approximately the same time of day for all visits (± 60 minutes) and always before noon (local time)
- IOP in both eyes
- Dilated ophthalmoscopy in both eyes
- Tomography (Pentacam®) for both eyes (at selected sites only) – may be performed prior to ophthalmoscopy while the subject is dilating

The Week 8 Visit will be the final visit, and the subject should be thanked for their participation in the study.

7.2.5 Unscheduled Visits

An unscheduled visit may be any visit to the Investigator other than the specific visits specified in the protocol as possibly required for the subject's ophthalmic condition.

The Investigator will perform all procedures necessary to evaluate the study participant at these visits and record any AEs in the CRF.

8. QUALITY CONTROL AND ASSURANCE

The progress of the study will be monitored by on-site, written, and telephone communications between personnel at the Investigator's site and the Study Monitor. The Investigator will allow the Sponsor or designee to inspect all CRFs, subject records (source documents), signed consent forms, study medication records (receipt, storage, preparation, and disposition), and regulatory files related to this study.

9. PLANNED STATISTICAL METHODS

9.1 General Considerations

Continuous study assessments will be summarized by treatment and time point (as applicable) using descriptive statistics (n, mean, median, standard deviation, minimum, and maximum). Categorical study assessments will be summarized by treatment and visit (as applicable) using frequency counts and percentages. Hypothesis testing, unless otherwise indicated, will be performed at a 2-sided 0.10 significance level. Where applicable, 2-sided 90% and 95% CIs will be reported. All p-values will be displayed to four decimal places, with p-values less than 0.0001 presented as '<0.0001' and p-values greater than 0.9999 presented as '>0.9999'. Difference between netarsudil QD and netarsudil BID will be calculated as netarsudil QD – netarsudil BID.

All study data will be listed by treatment, subject and time point (as applicable).

Statistical methods will be more fully described in a separate Statistical Analysis Plan.

9.1.1 Unit of Analysis

Safety endpoints will be analyzed for both eyes. For efficacy endpoints, the primary unit of analysis will be the study eye defined based on CCT of at least 600 μm evaluated by ultrasound pachymetry. If both eyes qualify based on CCT and enrollment criteria, the study eye will be the eye with the thinner cornea at the baseline. Qualified fellow eyes may also be summarized.

9.1.2 Missing Data and Intercurrent Events

The primary analysis will be completed with available data per subject from the mITT population. Robustness analyses will also be presented based on the multiple imputation methodology under different assumptions of missingness and intercurrent events (at random and not at random), using last observation carried forward (LOCF), and using the per protocol population with available data per subject.

Intercurrent events will be primary handled in the following manner:

1. Discontinuation of study medication and non-optimal compliance will be ignored, values measured after discontinuation of study medication or regardless of compliance will be used in the analyses [treatment policy strategy].

2. Withdrawal due to lack of efficacy or adverse events: missing data will be singly imputed as the worst within subject observation prior to the intercurrent event [hypothetical strategy].

3. Missing data without withdrawal or withdrawal due to reasons other than lack of efficacy or adverse events: missing data will be imputed employing Multiple Imputation (MI) using randomized treatment-based Markov Chain Monte Carlo (MCMC) methodology to impute non-monotone missing data and regression methodology to impute monotone missing data [hypothetical strategy].

9.1.3 Multiplicity Considerations

Adjustments for multiplicity will not be made in this early phase trial.

9.2 Hypotheses

H_{01}: The mean change from baseline CCT by ultrasound pachymetry in study eyes treated with netarsudil QD at Week 4 = 0.

H_{11}: The mean change from baseline CCT by ultrasound pachymetry in study eyes treated with netarsudil QD at Week 4 $\neq$ 0.

H_{02}: The mean change from baseline CCT by ultrasound pachymetry in study eyes treated with netarsudil BID at Week 4 = 0.

H_{12}: The mean change from baseline CCT by ultrasound pachymetry in study eyes treated with netarsudil BID at Week 4 $\neq$ 0.

9.3 Determination of Sample Size

This study is not powered to detect a pre-stated efficacy signal, but rather will be used to inform the design and power for any possible future studies. With a sample size of up-to 20 subjects per treatment group, the precision of the point estimate of mean change from baseline in CCT, as measured by the half-width of the two-sided 90% confidence interval (CI), will be approximately 1/2.7 of the standard deviation (SD) of the change from baseline, yielding 90% confidence that the true mean change from baseline is within ± SD/2.7 μm of the observed mean change from baseline. That is, if the SD of the change from baseline is 60 μm, then the half-width of the two-sided 90% CI would be 60 μm x 1/2.7 = 22.2 μm, yielding 90% confidence that the true mean change from baseline is within ± 22.2 μm of the observed mean change from baseline.

With a sample size of up-to 20 subjects within a treatment group, the study will have 80% power to reject H_{01} or H_{02} and in favor of H_{11} or H_{12} respectively and demonstrate a statistically significant mean change from baseline, assuming the true effect size (mean change / SD) is 0.577 or larger (e.g., assuming the true mean change from baseline is 34.6 μm and the standard deviation is 60 μm), a one sample t-test and a two-sided alpha = 0.10.

With a sample size of up-to 20 subjects per treatment group, the study will have 95% confidence of ruling out AEs with true incidence rates of 13.9% or higher within each treatment group. That is, with up-to 20 subjects in a treatment group, if an AE of a specific type is not observed, then with 95% confidence, the true incidence rate of that adverse event is less than 13.9%.

Similarly, with a sample size of up-to 40 subjects combined over treatment groups, the study will have 95% confidence of ruling out AEs with true incidence rates of 7.2% or higher within each treatment group. That is, with up-to 40 subjects in a treatment group, if an AE of a specific type is not observed, then with 95% confidence, the true incidence rate of that adverse event is less than 7.2%.

9.4 Analysis Populations

9.4.1 Modified Intent-to-Treat (mITT) Population

The mITT population will include all randomized subjects who have received at least one dose of study medication. This population will be the primary population for efficacy analyses and will be used to summarize a subset of efficacy variables and will summarize subjects as randomized.

9.4.2 Per Protocol (PP) Population

The PP population is a subset of the mITT population, which will include those subjects (and their visits) who do not have major protocol deviations likely to seriously affect the primary outcome of the study. This population will be the secondary population for efficacy analyses and will be used to summarize a subset of efficacy variables. If the PP and mITT populations are exactly the same, then additional efficacy analyses on the PP population will not be performed. The PP population will summarize subjects as treated.

9.4.3 Safety Population

The safety population will include all randomized subjects who have received at least one dose of investigational product. This population will be used to summarize safety variables and will summarize subjects as treated.

9.5 Demographics and Baseline Characteristics

Demographic and baseline characteristics such as age, gender, race, and ethnicity will be summarized and listed. Medical history, history of ocular surgery and procedures will also be summarized and listed.

9.6 Subject Disposition

Subject disposition will be presented in terms of the numbers and percentages of subjects who completed the study and discontinued from the study. Disposition will be summarized by treatment group and for all subjects.

The number of randomized subjects in each of the analysis populations (mITT, PP, and Safety) will be displayed by treatment.

The number and percentage of subjects who prematurely discontinue from the study and the reasons for study discontinuation will be summarized by treatment group for all subjects.

9.7 Primary Endpoint(s)

9.8 Efficacy Analysis

9.8.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the mean change from baseline in mean CCT as assessed by ultrasound pachymetry at Week 4.

9.8.2 Primary Efficacy Analyses

The primary comparisons in this trial will be within a treatment group on the mean change from baseline CCT to Week 4/Day 28 (Visit 4) for each of netarsudil QD and BID.
The primary efficacy endpoint change from baseline CCT will be summarized descriptively (n, mean, standard deviation, median, min, and max) and analyzed primarily using one-sample t-tests; comparisons between treatment groups will be completed using two-sample t-tests. Sensitivity analyses will be completed using Wilcoxon signed-rank tests within a treatment group, Wilcoxon rank sum tests between treatment groups and an ANCOVA model with terms for baseline CCT value, treatment. The least squares mean will be presented for each treatment group from the model together with two-sided p-values and 90 and 95% confidence intervals around the change from baseline within each treatment group. Comparisons between treatment groups on the change from baseline CCT will also be made including the least squares mean difference and corresponding two-sided p-values and 90 and 95% confidence intervals.

The primary analysis will use the mITT population with available data per subject. Robustness analyses will also be presented based on the multiple imputation methodology under different assumptions of missingness and intercurrent events (at random and not at random), using last observation carried forward (LOCF), and using the per protocol population with available data per subject.

Intercurrent events will be primary handled in the following manner:

1. Discontinuation of study medication and non-optimal compliance will be ignored, values measured after discontinuation of study medication or regardless of compliance will be used in the analyses [treatment policy strategy].

2. Withdrawal due to lack of efficacy or adverse events: missing data will be singly imputed as the worst within subject observation prior to the intercurrent event [hypothetical strategy].

3. Missing data without withdrawal or withdrawal due to reasons other than lack of efficacy or adverse events: missing data will be imputed employing Multiple Imputation (MI) using randomized treatment-based Markov Chain Monte Carlo (MCMC) methodology to impute non-monotone missing data and regression methodology to impute monotone missing data [hypothetical strategy].

9.8.3 Secondary Efficacy Endpoints

Secondary endpoints include:

- Mean change from baseline in BCVA at Week 4
- Mean change from baseline in CCT as assessed by ultrasound pachymetry at Week 8
- Mean change from baseline in BCVA at Week 8
- Proportion of subjects who gained ≥15 letters (3 lines) in BCVA at Week 4
- Proportion of subjects who gained ≥15 letters (3 lines) in BCVA at Week 8
- Proportion of subjects with complete resolution of corneal edema at Week 4
- Proportion of subjects with complete resolution of corneal edema at Week 8

9.8.4 Secondary Efficacy Analyses

The secondary efficacy analyses will be conducted in the mITT population with available data per subject. Descriptive statistics will be presented by treatment group. Summarization and analysis of the mean change from baseline in BCVA at Weeks 4 and 8 and mean change from baseline in CCT by ultrasound pachymetry at Week 8 will be completed using a similar strategy as for the primary endpoints.

Testing of the proportion of subjects who gained ≥15 (3 lines) in BCVA at Weeks 4 and 8 (separately) and the proportion of subjects with complete resolution of corneal edema at Weeks 4 and 8 (separately) will be completed using logistic regression with fixed effects of treatment and corresponding baseline measure.

The adjusted odds ratios and marginal proportions and difference in proportions along with corresponding two-sided 95% Confidence Intervals (CIs) and p-values will be presented.

Treatment comparisons will also be made using Pearson's chi-squared test or Fisher's exact test if any of the cell counts are less than five as a sensitivity analysis.

The primary analyses of the secondary endpoints will use the mITT population with available data per subject. Robustness analyses may also be presented based on the multiple imputation methodology under different assumptions of missingness and intercurrent events (at random and not at random), using last observation carried forward (LOCF), and using the per protocol population with available data per subject.

9.8.5 Exploratory Efficacy Endpoints

Exploratory endpoints include:

- Proportion of subjects who gained ≥15 letters (3 lines) in BCVA at Week 2
- Proportion of subjects who gained ≥10 letters (2 lines) in BCVA at Weeks 2, 4, and 8
- Proportion of subjects who gained ≥5 letters (1 line) in BCVA at Weeks 2, 4, and 8
- Mean change from baseline in CCT as assessed by Pentacam® at Week 4 (selected sites only)
- Mean change from baseline in V-FUCHS glare factor score at Week 4

9.8.6 Exploratory Efficacy Analyses

Exploratory endpoints will be analyzed in a similar manner as the secondary endpoints.

9.8.7 Primary Safety Assessments and Analyses

Adverse events (AEs) will be coded using the MedDRA dictionary. Frequencies and percentages of treatment-emergent adverse events (TEAEs) will be summarized at the subject level by system organ class and preferred term for all TEAEs, treatment related TEAEs, serious TEAEs, and TEAEs causing premature treatment discontinuation by treatment group. An AE is treatment emergent if it occurs or worsens after the first dose of study medication. Similar summaries will be presented for all TEAEs by maximal severity. Separate summaries will be performed for ocular and non-ocular AEs.

Best corrected visual acuity and intraocular pressure data for both the study eye and the fellow eye will be summarized for each measured visit and for change from baseline to each post-treatment visit using the continuous summary statistics.

Anterior segment biomicroscopy and ophthalmoscopy measures will be summarized at each measured visit using discrete summary statistics. Additionally for anterior segment biomicroscopy, discrete summaries will be provided by region, finding, visit, time point, and eye (study eye and fellow eye) for the number of subjects with at least one severity grade increase from baseline and for the number of subjects judged to be clinically significant by the Investigator. Shift tables from baseline may also be summarized.

Vital signs will be summarized at each measured visit and for change from baseline to each measured visit using continuous summary statistics by treatment group and visit.

10. ADMINISTRATIVE CONSIDERATIONS

10.1 Investigators and Study Administrative Structure

The Principal Investigator is responsible for all site medical-related decisions. The qualified Sponsor Medical Monitor is responsible for the safe conduct of this study. The contact information of the Sponsor Medical Monitor is as follows:

Richard A. Lewis, MD
Phone: (916) 768-7703
Email: rlewis@aeriepharma.com

10.2 Institutional Review Board (IRB) or Independent Ethics Committee (IEC) Approval

This protocol, materials used to recruit subjects, and materials used to document consent must be approved by the IRB/IEC prior to initiation of the study. The name and address of each reviewing IRB/ IEC will be documented in the Trial Master File. Written IRB/IEC approval must adequately identify the protocol and informed consent. In addition to approving the protocol, the IRB/IEC must also approve the Subject Information and Consent Form, as well as any advertising tools that will be used for the study. Written approval also must indicate whether approval was granted based on full committee review or expedited review. Copies of all approved materials, all correspondence with the IRB/IEC and written approval from the IRB/IEC must be made available to the Sponsor, prior to the start of subject enrollment into the study. The Investigator will report promptly to the IRB/IEC any new information that may adversely affect the safety of the subjects or the conduct of the study. The Investigator will submit written summaries of the study to the IRB/IEC as required. On completion of the study the IRB/IEC will be notified that the study has ended.

10.3 Ethical Conduct of the Study

The study will be conducted according to this clinical protocol and will be governed by the following directives and guidelines:

- US CFR, Title 21
- ICH – Consolidated Good Clinical Practices Guideline (E6)
- Standard Operating Procedures (SOPs) of the Sponsor and any vendors participating in the conduct of the study
- The ethical principles that have their origin in the Declaration of Helsinki

10.4 Subject Information and Consent

Written informed consent will be obtained from each subject before any subject specific procedures are initiated. A copy of the signed and dated consent document will be given to each subject. The original signed and dated informed consent document must be maintained in the study files at the Investigator's site.

The Investigator is responsible for ensuring that no subject is subject to any study-related examination or activity before that subject has given informed consent. The subject must give written consent after the receipt of detailed information. The verbal explanation will cover all the elements specified in the written information provided for the subject.

It should be emphasized that the subject is at liberty to withdraw consent to participate at any time, without penalty or loss of benefits to which the subject is otherwise entitled.

Subjects who refuse to give, or withdraw, written informed consent may not be included or continued in this study, but this will not impact on their subsequent care.

The Investigator will inform the subject of the aims, methods, anticipated benefits and potential hazards of the study, including any discomfort it may entail. The subject must be given every opportunity to clarify any points he/she does not understand and if necessary, ask for more information. At the end of the interview, the subject may be given time to reflect if this is required, or if the subject requests more time. Subjects and/or legal guardian will be required to sign and date the informed consent form.

Signed informed consent must be attained prior to the conductance of any study procedures.

10.5 Subject Confidentiality

The Investigator and his/her staff will maintain all personal subject data collected and processed for the purposes of this study using adequate precautions to ensure confidentiality, in accordance with local, state and federal laws and regulations.

Monitors, auditors and other authorized representatives of the Sponsor, the IRB/IEC approving this study, and government regulatory authorities (e.g., FDA) may be granted direct access to the study subject's original medical and study records for verification of the data or clinical study procedures. Access to this information will be permitted to representatives of the aforementioned organizations to the extent permitted by law.

A report of this study's results may be published or sent to the appropriate health authorities in any country in which the study medication may ultimately be marketed, but subject identities will not be disclosed in these documents.

10.6 Study Monitoring

Clinical research associates hired or contracted by the Sponsor will be responsible for monitoring the study sites and study activities. Clinical research associates will contact and visit the Investigator regularly. The actual frequency of monitoring visits depends on subject enrollment and on study site performance. Among others, the following items will be reviewed:

- Study progress
- Compliance with the protocol
- Completion of eCRFs
- Dispensing, storage, and accountability of study medication
- Source data verification
- AE and SAE reporting
- Essential documents contained within the Investigator's site file

For source data verification (i.e., comparison of eCRF entries with subject records), data will be 100% source verified and will include at a minimum:

- Subject identification
- Informed consent (procedure, signature, and date)
- Selection criteria
- Primary efficacy and safety parameters (i.e., AEs)

Member(s) of the Sponsor or their designee, in the role of Clinical Research Associate, will meet with the Investigator prior to the initiation of the study in order to assess the adequacy of the Investigator's subject population, facilities, and equipment, and to familiarize the Investigator with the protocol.

The Clinical Research Associate will subsequently meet with the Investigator after several of the subjects have initiated the study in order to ensure that the subjects are being properly selected, that adequate supplies for the study have been provided and that the assignment of medication is properly recorded. In addition, the Clinical Research Associate will verify that the Investigator follows the approved protocol and all approved amendments, if any, by reviewing the Investigator's regulatory documents, source documents, ICFs, and eCRFs of study subjects.

The Clinical Research Associate will meet with the Investigator when all subjects have completed the Final Visit of the study, in order to collect unused study medications and unused supplies and materials.

Interim monitoring visits and telephone consultations will be done by the Clinical Research Associate as necessary, to ensure the proper progression and documentation of the study.

10.7 IRT

Interactive response technology (IRT) activities will be performed as described in the IRT User Manual.

10.8 Case Report Forms and Study Records

The initial point of entry of study data should be the subject source documentation.
The location and nature of the source documentation for all data collected in the study will be identified in the study files at the Investigator's site. In cases where no source documents will be used (i.e., data will be recorded directly into the eCRF without first being recorded on another document, such as a flowsheet, laboratory report, or other typical form of data reporting for later transcription to the eCRF), the original data will be included in the eCRF.

Source document information should be legible. Recorded data should only be corrected by drawing a single line through the incorrect entry and writing the revision next to the corrected data. The person who has made the correction should place his or her initials as well as the date of the correction next to the correction. Data may not be obliterated by erasure, redaction, or with correction fluid.

Study data will be transcribed and recorded via an electronic data capture (EDC) system as eCRFs. Security and authorization procedures consistent with the EDC system must be used. At each subject visit, the appropriate eCRFs must be completed. Whenever an eCRF is used, be sure to provide all information requested including subject identification number and initials, name or number of Investigator, date(s), etc. All applicable questions should be answered, and all data requested should be provided. Those areas that require a response but are not filled in correctly are considered incomplete or erroneous entries and will have to be corrected.

Each authorized study staff member will receive a unique access account in order to use the EDC system. Access accounts will not be shared among study staff. Authorized users will make entries and/or changes to eCRFs via a secure internet access. Each completed set of eCRFs will be reviewed by the Investigator who will then electronically sign and date the eCRF confirming that data for the subjects are complete and accurate.

The study records must include a copy of each Investigator's CV and medical license, and statement of Investigator qualifications. The name of each Sub-Investigator working under the supervision of the Investigator is also required to be filed in the study records.
In addition, each eCRF, subject charts/source documents, IB, protocol, protocol amendments,

correspondence with the Sponsor/designee and the IRB/IEC, study medication storage, receipts, returns and dispensing records, Delegation of Responsibilities Log, site training records, records of site monitoring, any unmasking documentation, AE and SAE reporting, IRB/IEC approvals, advertisements, written information provided to subjects, and subject completed ICFs will be included in the study records.

If the Investigator moves, withdraws from an investigation, or retires, the responsibility for maintaining the records may be transferred to another person (e.g., Sponsor, other Investigator) who will accept the responsibility. Notice of this transfer, including written acceptance, must be made to and agreed upon by the Sponsor.

10.9 Protocol Deviations

Per ICH E6 (GCP) R2 Section 4.5.1 the Investigator/institution should conduct the trial in compliance with the protocol agreed with the sponsor and, if required, by the Regulatory Authority and which was given approval/favorable opinion by IRB/IEC.

Protocol waivers or deviations from the protocol inclusion and exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study regulatory acceptability or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

The site will contact the Sponsor for clarification of inclusion and/or exclusion criteria as needed prior to enrollment of the study subject. The Sponsor will document clarification requests and responses or their representative. If a subject does not meet all the inclusion and exclusion criteria during screening, that subject may not be enrolled into the study.

If a protocol deviation is identified by the Investigator or through site monitoring activities an immediate submission to the IRB/IEC may be required e.g., 24 or 48 hours (as per IRB guidelines). The Sponsor will assess any protocol deviation and decide whether any of these non-compliances should be reported to the relevant competent authority as a serious breach of GCP and the protocol. If per the relevant competent authorities' requirements, the protocol deviation is not required to be reported immediately but is still required to be notified to the IRB/IEC, the specific protocol deviation will be added to the annual progress report.

The Sponsor will review, designate, and/or approve all protocol deviations prior to the database lock.

10.10 Access to Source Documentation

The Investigator will permit study-related monitoring visits, audits, IRB/IEC review, and regulatory inspection(s) by providing direct access to source data and documents.

The monitor and the head of the medical institution (where applicable) agrees to allow the monitor direct access to all relevant documents and to allocate their time and the time of their staff to monitor to discuss findings and any issues.

Sponsor/designee will monitor the study to ensure:

- Data are authentic, accurate and complete.
- Safety and rights of the subjects are being protected.
- Study is conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP and all applicable regulatory requirements.

10.11 Data Generation and Analysis

After data have been entered into the study database, a system of computerized data validation checks will be implemented and applied to the database. Query reports pertaining to data omissions and discrepancies will be forwarded to the clinical Investigator and the Sponsor for resolution. The study database will be updated by the clinical Investigator or their staff, in accordance with the resolved query reports. All changes to the study database will be documented.

10.12 Retention of Data

The Investigator's site will retain all records related to the study in compliance with ICH Good Clinical Practices Guidelines E6 (R2) Section 4.9.4.

Archived versions of the database will be saved by the Sponsor consistent with ICH Good Clinical Practices Guidelines E6 (R2) Section 5.5.11, complying with whichever of the requirements is longer. The Sponsor will notify the Investigator when study records should be destroyed.

10.13 Financial Disclosure

The Principal Investigator and Sub-Investigators (as listed on Form FDA 1572) will provide financial disclosure information prior to participation in the study. The Principal Investigator and any Sub-Investigators will notify the Sponsor promptly of any required revision to their financial disclosure status during the term of this study, annually, or at the end of the study (if applicable) and 1-year post-study completion. The Principal Investigator and Sub-Investigators will provide updated financial disclosure information upon the Sponsor's written request following completion of the study.

10.14 Publication and Disclosure Policy

Aerie Pharmaceuticals, as the Sponsor, has proprietary interest in the study. Authorship and manuscript composition will reflect joint cooperation between multiple Investigators and sites and Aerie Pharmaceuticals personnel. For studies with multiple centers, no individual publications will be allowed prior to completion of the final report of the multicenter study except as agreed with Aerie Pharmaceuticals.

11. AMENDMENT SUMMARY OF CHANGES

11.1 Amendment 1: 03 February 2021

Section(s)	Original	Amendment 1	Rationale
4.3 Exclusion Criteria	2. Concurrent or anticipated need for treatment for FCD, e.g., Muro 128 (2% or 5%) during the course of the study	2. Concurrent or anticipated need for treatment for FCD, e.g., Muro 128 (2% or 5%) during the course of the study **in the study eligible eye(s)**	Reduce medication restrictions for non-study eye
4.3 Exclusion Criteria	11. Concurrent or anticipated use of topical corticosteroids applied to the ocular surface or in the vicinity of the eyes (including intranasal corticosteroids and topical corticosteroids applied to the face)	11. Concurrent or anticipated use of topical corticosteroids in the study eligible eye(s)	Reduce medication restrictions for non-study eye
4.3 Exclusion Criteria	12. History of prior treatment with netarsudil (monotherapy or in combination)	12. History of prior treatment with netarsudil (monotherapy or in combination) or any other Rho Kinase inhibitor	Clarify exclusion criteria
4.3 Exclusion Criteria and 5.6.1 Prohibited Interventions	16. Concurrent or anticipated use of corticosteroids during the study (with the exception of intraarticular corticosteroids and topical corticosteroids applied anywhere other than the eyes or face – see Exclusion #10). Individuals currently using corticosteroids must have been on a stable dose for at least 30 days prior to the Screening Visit, and the dose must not be anticipated to change during the course of the study	16. Concurrent or anticipated use of **systemic** corticosteroids during the study. Individuals currently using **topical or other locally acting corticosteroids (with the exception of use in the study eligible eye[s])** must have been on a stable dose for at least 30 days prior to the Screening Visit, and the dose must not be anticipated to change during the course of the study	Reduce medication restrictions
6.3 Concomitant Medication Assessments	However, medications used as part of the intravitreal injection process other than topical or subconjunctival anesthetic and povidone iodine swabs (e.g., pre- or post-injection antibiotics or IOP-lowering medications) should be recorded on the eCRF.	[removed]	This statement is not necessary for this study
6.7.4 V-FUCHS Questionnaire	N/A	Subjects who are not fluent in the English language may be exempt from completing this questionnaire.	Clarification - There are currently no validated translations of the V-FUCHS questionnaire

6.9.1 Performing Adverse Event (AE) Assessments	Investigators are asked to use the verbatim term "conjunctival hyperemia" on the study AE form to describe observations of conjunctival redness if the ocular redness observation is increased from baseline observations and clinically meaningful. Investigators are also asked to note all observations of new or worsening conjunctival hyperemia on the biomicroscopy eCRF as well as on the study AE form.	Investigators are also asked to note all observations of new or worsening conjunctival hyperemia on the biomicroscopy eCRF as well as on the study AE form **if deemed necessary (per Investigator discretion).**	Clarification
6.9.6.1 Reporting SAEs, SSARs or SUSARs	N/A	The contact information of the study Safety Mailbox is as follows: Covance PSS SAEintake@covance.com Fax: 1-888-887-8097	Adding to / updating safety reporting information
6.9.7 Pregnancy Reporting	While pregnancy itself is not considered to be an AE or SAE, pregnancy reports are tracked by the study Medical Monitor. The Investigator must complete the pregnancy report form and email the form to the study Medical Monitor within 1 business day of knowledge of the pregnancy. Following delivery or termination of pregnancy, the pregnancy report form is to be completed and submitted by fax or email to the Medical Monitor for the study.	While pregnancy itself is not considered to be an AE or SAE, pregnancy reports are tracked by **Covance and** the study Medical Monitor… The Investigator must complete the pregnancy report form and email the form to the study **Safety Mailbox** within 1 business day of knowledge of the pregnancy. Following delivery or termination of pregnancy**, the updated or follow-up** pregnancy report form is to be completed and submitted by fax or email to the **Safety Mailbox** for the study.	Adding to / updating safety reporting information
9.1.1 Unit of Analysis	Qualified fellow eyes will also be summarized.	Qualified fellow eyes **may** also be summarized.	Updating plan for potential posthoc analysis

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